Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1933–1943, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00
© 1990 Pergamon Press plc

Reproductive Factors and Cancers of the Breast, Ovary and Endometrium

SILVIA FRANCESCHI

Epidemiology Unit, Aviano Cancer Center, Via Pedemontana Occidentale, 33081 *Aviano (PN), Italy*

Abstract—*In contrast to cancers of non-hormone-dependent sites, cancers of the breast, ovary and endometrium show a slowing down of the rate of increase in incidence at around age 50, as if ceasing menstrual activity reduced risk. Also nulliparous women appear more prone to these three cancers as compared to parous women, thus suggesting that pregnancies also represent a 'protected' time. Epidemiological studies on breast cancer, the only ones sufficiently large to try to disentangle meaningfully the effects of collinear reproductive variables such as parity and ages at first and last birth, show, however, that the effect of pregnancy is not simple and depends on how many births take place and at what age. Larger population-based investigations able to obtain with greater precision information not only on reproductive factors but also on possible confounding variables (e.g. socio-economic status, dietary habits, etc.) are mandatory, particularly as regards ovarian cancer and endometrial cancer. The lesson from the recent studies on pregnancy-related events and breast cancer is, however, that initially a decrease of old certainties must be expected to derive from the accumulation of new, better epidemiological data.*

INTRODUCTION

CANCERS of non-hormone-dependent sites (e.g. colon cancer, Fig. 1) show a more than 100-fold increase in incidence between the ages of 25 and 70 [1]. The relationship between incidence, I, age, a, and time, t, can be represented by the equation

$$I(t) = at^k$$

where the exponent of age, k, is usually between 4 and 5. Although in the past this increase in incidence with increasing age was often attributed to a direct effect of aging, it is now believed to be the effect of duration of 'exposure' to some relevant carcinogens (e.g. cigarette smoking).

Hormones are not mutagens but they can affect 'initiation' of a cancer by altering the probability of a DNA-damaging event becoming fixed through their effect on cell-cycle time [2]. Furthermore, they have a well-established role in 'promotion' in certain animal experimental systems [3].

Hormones and growth factors involved in menstrual activity are the likeliest candidates for the etiology of cancers of the breast, ovary and endometrium, as suggested by the age-specific incidence curves of such malignancies (Fig. 1). The curves in Fig. 1 are not identical and must be interpreted cautiously: any variation of cancer incidence or, as regards ovary and endometrium, of prevalence of oophorectomy and hysterectomy can distort them. However, in sharp contrast with most common epithelial malignancies, they all show a clear slowing down of the rate of increase around menopause, as if ceasing menstrual activity (i.e. menopause) reduced risk.

Consistently, many analytic studies showed that an early start of menstrual activity (i.e. menarche) increases risk of cancers of the breast, ovary and endometrium [1, 4]. The association between an early age at menarche and an increased risk of hormone-dependent cancers is generally weak, sometimes restricted to some subgroups (mostly premenopausal women) or even lacking in some data sets, but serious recall problems, especially in elderly women, may partly account for this [1]. Also nulliparous women appear to be more prone to cancers of the breast, ovary and endometrium as compared to parous women, thus suggesting that pregnancies also represent a sort of 'protected time'.

The real factors associated with such menstrual and reproductive events remain, however, largely obscure. It may be that pregnancy is truly protective or that some women who are unsuccessful at getting pregnant are at increased cancer risk. Furthermore, the effect of parity seems to depend, particularly as regards breast cancer, on the age at which the first

Accepted 10 June 1989.
Paper presented at the 7th Annual ECP Symposium 'Breast, Endometrial and Ovarian Cancer: Aetiological and Epidemiological Relationships', Bilthoven, The Netherlands, 1–2 May 1989.

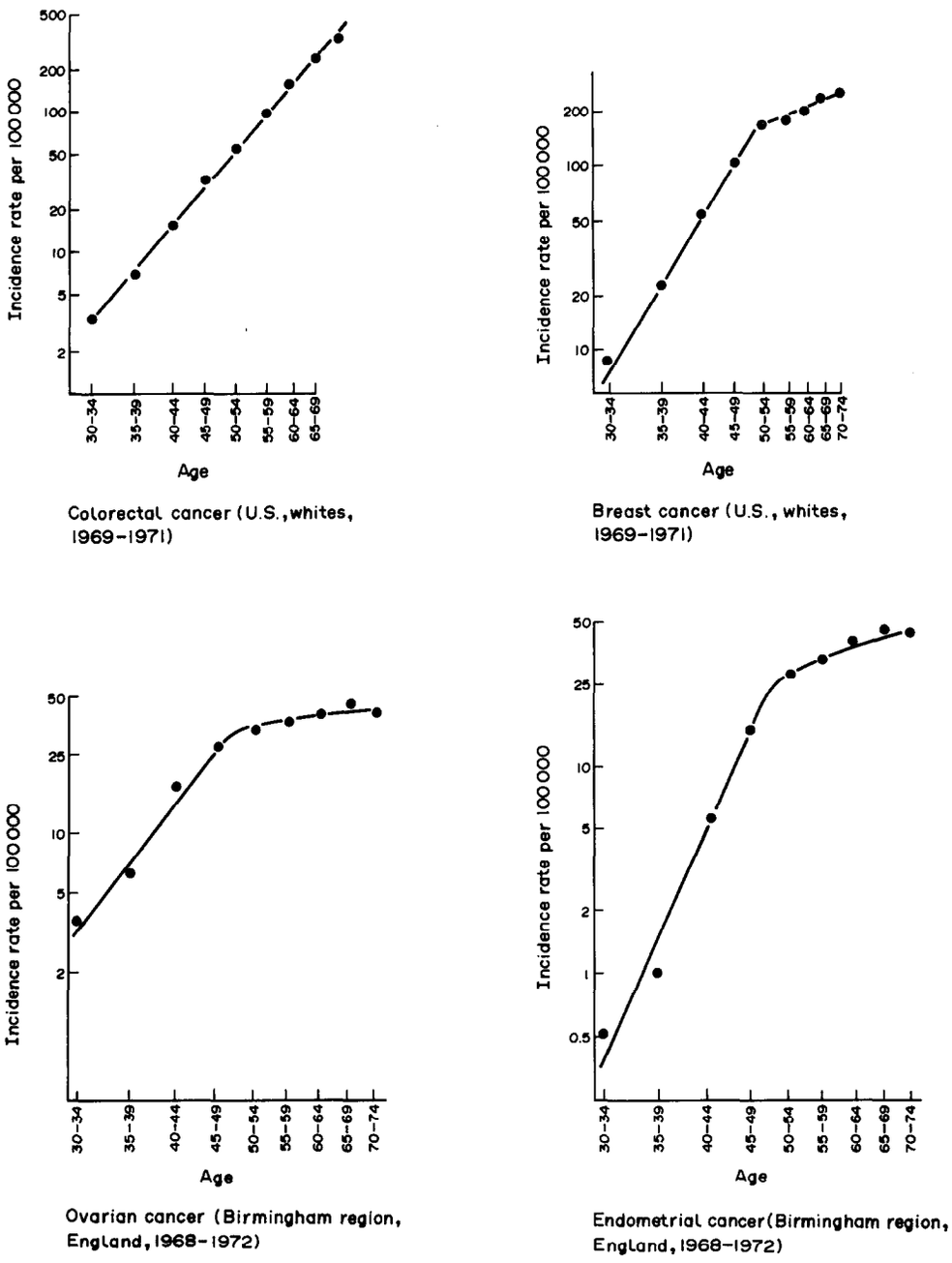

Fig. 1. Age-specific rates for various cancers in women.

and, perhaps, subsequent pregnancies take place and whether they end with a full-term delivery [4].

The epidemiological evidence on the relationship between reproductive factors and risk of cancers of the breast, ovary and endometrium will be reviewed. Special attention will be paid to those aspects (i.e. age at first birth and last pregnancy, and lactation) whose role is still controversial but may provide us with further insights into the function of female hormones.

BREAST CANCER

Among the three female cancers under examination in the present review, breast cancer is by far the one which has been the subject of the highest number of studies. Some of them have included thousands of subjects and have also been pooled in extremely large meta-analyses. It is therefore the only hormone-dependent cancer in which attempts to disentangle the effects of collinear variables, such as parity, age at first and subsequent pregnancies, etc., have been pursued meaningfully. The emerging picture is, however, far from clear and some pregnancy-related risk factors have been reported, refuted and again reaffirmed in succession [4].

Parity and age at first birth

Low parity has been suspected of being a risk factor for breast cancer for more than two centuries

Table 1. *Characteristics of* 26 *studies which examined the relationships between breast cancer and reproductive factors* [6]

	Significant associations			
	Age at first birth only	Parity only	Age at first birth and parity	None
Type of study:				
Hospital-based case-control	3	1	5	
Population-based case-control	—	5	2	1
Screening program	3	—	3	
Other	1	—	2	
Age upper limit:				
<60 years	1	2	3	
≥60 years	5	4	8	1
Unknown	1	—	1	
Location of study:				
North America	2	—	5	1
North Europe	2	3	3	
South Europe	2	—	2	
Developing countries	—	2	2	
Other	1	1	—	
Number of breast cancer cases:				
<500	4	4	3	1
≥500	3	2	9	
Total	7	6	12	1

[4]. Overall, breast cancer incidence in nulliparous women appears to be about 50% higher than in parous women [4].The causality of this association, however, tended to be dismissed by the observation, from an international cooperative study conducted in seven areas of the world [5], that earlier age at first birth could explain the apparent relation between breast cancer and parity. The debate is still open.

A recent review [6] examined 26 published studies which included information on parity and age at first birth. One of them [7] found no significant association with either variable, seven [5, 8–13] showed an association between breast cancer and age at first birth but not parity, and six [14–19] an association with parity but not age at first birth. In 12 studies [20–32] both variables were independently related with breast cancer risk. As shown in Table 1, the discrepancies were not easily explainable from the known characteristics of the studies under consideration (country, criteria for selection of cases and controls, age of subjects, etc.) nor was it possible to dismiss the role of chance (most results were not significantly heterogeneous [6]). It is, however, worth noting that the largest investigations found significant associations with both age at first birth and parity, whereas five out of six of those where no relation between breast cancer and age at first birth emerged were population-based case-control or cohort studies. Kvale *et al.* [33] reported a relation between early age at first pregnancy and high mortality for cardiovascular and other common non-cancer causes of death. Thus they suggested that in case-control studies, recruiting controls among patients with other diseases the cancer risk related to late age at first pregnancy may tend to be overestimated.

Biologically, pregnancies, at least those of more than 5-month duration, may induce a lifelong decrease in the risk of breast cancer either by (1) making the breast tissue less susceptible to carcinogens or promoters, or (2) influencing production of hormones or growth factors (e.g. prolactin, estrogens, etc.) permanently, or (3) affecting immunological resistance [1, 4, 27, 28]. The association between early age of first birth and risk is less well understood, but does not seem to be accounted for by a confounding factor which reduces fertility and thereby delays pregnancy [34]. The formation of 'precancerous' lesions may be slowed down by the terminal differentiation of mammary gland epithelium generated by an early first pregnancy [35].

Subsequent pregnancies

In a re-analysis [36] of the classical study by MacMahon *et al.* [5], it was shown that not only was age at first birth a risk factor for breast cancer (with approximately a 3.5% increase of relative risk for every year of increase in age at first birth) but also age at any subsequent birth after the first affected risk in an independent and statistically

Table 2. Breast cancer and ages at first and last birth in Norway [28]

		Model 1*	Model 2*	Model 3*
Age at first birth (≥35 vs. <20 years)	Relative odds estimate	1.77	1.33	1.05
	P values for linear trend	<0.001	0.03	0.79
Age at last birth (≥40 vs. <25 years)	Relative odds estimate	0.97	1.38	1.47
	P values for linear trend	0.80	0.01	0.06

*Estimate from multiple logistic regression allowance was made for:
Model 1: age at first or last birth, age and urban–rural place of residence;
Model 2: age at first or last birth, age, urban–rural place of residence and parity;
Model 3: age at first and last birth, age, urban–rural place of residence and parity excluding women with <2 full-term deliveries.

significant way (approximately 0.9% increase of relative risk for every year of increase in age at every birth). Interestingly, the age of approximately 35 years seemed to represent for every birth a critical point: before this age any full-term pregnancy confers some degree of protection; after this age any full-term pregnancy appears to be associated with an increase in breast cancer risk [36]. Biologically, the possibility that pregnancy could be capable of accelerating the growth of an existing breast cancer in subclinical phase is still debated [37].

That the relation between age at any pregnancy and breast cancer risk may be more complex than previously believed was further suggested by the finding of the already mentioned prospective study conducted in Norway [28], where the association between early age at first birth and low risk of breast cancer was removed after adjustment for age at last birth (Table 2). Age at last birth, which had not often been regarded as an important risk factor in the past, did not show any association with breast cancer until adjustment for parity was performed [28]. This may explain the lack of association in previous investigations [4] in which allowance for parity and other reproductive variables was insufficient. Furthermore, despite the overall association between increasing parity and lower risk, in the study by Kvale *et al.* [27, 28] not only women with many late pregnancies but also those with few, widely spaced pregnancies had a higher risk than nulliparous women, indicating that both the age when pregnancy occurs and the length of intervals between successive births may be relevant.

Large and still partly unexplained differences in breast cancer incidence between different countries, socio-economic classes and birth cohorts [4] may be better understood allowing not only for the simplest reproductive factors but also for the global pattern of child-bearing and age at breast cancer diagnosis. If pregnancies cause a transient increase in the risk of breast cancer followed by a subsequent decrease [4], the adverse effect would primarily become evident for cancers in the very young and for cancers in the higher age groups when many pregnancies occur late in the reproductive period.

Lactation and abortions

Three recent articles [31, 38, 39] and a few earlier studies [9, 11, 40–50] have shown an independent beneficial effect of lactation on risk of breast cancer, at least in premenopausal women. Studies where the influence of breast-feeding could be assessed after other reproductive characteristics had been taken into account are summarized in Table 3. The investigation conducted in Shanghai [31] is of special interest since a very large cumulative number of nursing months allows for more precise estimates of the effect of lactation than those obtained from most previous investigations. Relative to women whose total nursing time was under 3 years, long-term nursing mothers (more than 9 years) exhibited a 63% reduction in risk of breast cancer.

Lactation may exert a protective effect on the breast in different ways: (1) hormonal changes (e.g. increased prolactin and decreased estrogen production), (2) inhibition of ovulation (1 year of lactation results, on the average, in 8.1 months of anovulation [31]) and (3) mechanical 'flushing-out' of carcinogens. Alternatively, as suggested by Byers *et al.* [38], women who are not able to lactate may have some underlying hormonal aberration that might be responsible for an increased risk of breast cancer. Large doses of estrogen at parturition, given to prevent lactation, might also play a part.

Epidemiological studies have been inconsistent with their findings relating pregnancies of less than 5 months duration to breast cancer risk. Some studies [7, 51], concentrating on breast cancer risk following a first trimester abortion, either spontaneous or induced, found an increased risk. Pregnancy is accompanied initially by proliferation but is then followed by marked differentiation of mammary epithelial cells [4]. If the pregnancy is inter-

Table 3. Breast cancer and lactation: summary of studies where parity and/or age at first birth were taken into account

Author(s)	Study location	Relative risk estimates Age <50	Age ≥50	All
Kaplan and Acheson [40]	U.S.A.	—	—	0.81
Salber *et al.* [41]	U.S.A.	1.14	1.09	1.11
Valaoras *et al.* [42]	Greece	0.84	1.27	1.02
Ravnihar *et al.* [43]	Yugoslavia	0.80	0.67	0.72
Lin *et al.* [44]	Taiwan	0.87	1.55	1.04
Yuasa and MacMahon [45]	Japan	0.80	2.14	1.06
Lowe and MacMahon [46]	U.K.	1.06	1.12	1.10
Mirra *et al.* [47]	Brazil	0.73	0.93	0.81
Kalache *et al.* [48]	U.K.	0.92	—	—
Lubin *et al.* [49]	Canada	0.60	0.60	0.60
Anderson [50]	South Africa	0.52	0.96	0.68
MacMahon *et al.* [9]	U.S.S.R.	0.99	0.45	0.69
Brinton *et al.* [11]	U.S.A.	—	—	0.94
Byers *et al.** [38]	U.S.A.	0.60	0.89	—
McTiernan and Thomas* [39]	U.S.A.	0.45	0.38	—
Yuan *et al.** [31]	China	—	—	0.37

*Long-term lactation.

rupted during the first trimester, the risk of breast cancer may be increased and this may have heavy consequences, from a public health viewpoint, since an increasing number of abortions are taking place before first full-term pregnancy in many countries [4].

OVARIAN CANCER

Epithelial ovarian cancer is approximately four-fold rarer than breast cancer and presents substantially greater diagnostic difficulties and a worse prognosis. Epidemiological studies have been fewer as compared to those on breast cancer, and have included smaller numbers of women. This obviously hampers the possibility of drawing reliable conclusions concerning the independent role of reproductive factors closely linked with each other, and the differential effect on specific subgroups of patients (e.g. pre- and post-menopausal women, different tumor cell-type of origin, etc.).

Number of pregnancies

Nulliparity and, even earlier, single marital status (see Wynder *et al.* [52]) have been very consistently related to a high risk of ovarian cancer. A strong inverse association between completed family size and mortality from ovarian cancer in different countries and for successive cohorts in the same country has been reported [53]. In contrast to breast cancer, there is no evidence of any dual effect of pregnancy according to age at pregnancy: at no age do nulliparous women seem to be at a lower risk as compared to parous women.

The most debated issue is whether nulliparity and low parity *per se* or difficulty in conceiving facilitate the development of ovarian cancer. Unfortunately, infertility cannot be measured accurately in most epidemiological studies [54]. Many infertile women do not seek medical care for this problem, even more women receive only an incomplete and inconclusive evaluation of the causes of their infertility and/or are unable to report accurately on them.

Some studies suggest, however, that pregnancies exert *per se* a favorable influence on risk of ovarian cancer. Of 20 studies that have examined the question [52, 55–72], a few [55–57, 60–71] showed a further decline in risk associated with full-term pregnancies beyond the first, thus suggesting that additional risk reduction was conferred by events accompanying each pregnancy. Table 4 summarizes relative risk estimates from all studies allowing an assessment of the effect of numbers of pregnancies and age at first pregnancy in parous women only [52, 55, 57–59, 62–68, 70–72]. Investigations which included, as a control group, other hormone-dependent female tumors were not considered. It is clear that reduction in risk deriving from pregnancies beyond the first is very weak. Partly on account of limited study sizes, it reached statistical significance in only three investigations [59, 62, 71].

Results on the influence of incomplete pregnancies, either terminated with a voluntary or spontaneous abortion, are inconclusive. Some authors [71], however, reported that the risk of ovarian cancer was also weakly lowered among women having experienced an abortion.

Age at first pregnancy

The suggestion that early age at first pregnancy may also protect against ovarian cancer came from

Table 4. Studies on ovarian cancer reporting relative risk estimates for both parity and age at first birth

Author(s)	Parity					Age at first birth (years)				
	1	2	3	4	5	<20	20–24	25–29	30–34	≥35
Wynder *et al.* [52]	1*	0.8	0.8	1.2	0.8					
Joly *et al.* [55]	2.1		1.3		1*	1*	1.4		2.3	
Casagrande *et al.* [57]	1*			0.8						
MacGowan *et al.* [58]	1*		1.6		0.3†	1*	0.7		1.4	
Hildreth *et al.* [59]	1*	0.6	1.0	0.5†		1*	1.9	3.0†	2.5†	
Cramer *et l.* [62]										
—unadjusted	1*		0.5†		0.5†	1*		1.1	1.2	
—adjusted‡	1*		0.5†		0.5†	1*		1.0	1.0	
Risch *et al.* [63]	1*			0.8						
La Vecchia *et al.* [64]										
—unadjusted	1.9		1.7	1*		1*	2.7†	3.2†	4.0†	
—adjusted‡	1.3		1.2	1*		1*	2.5†	2.8†	3.3†	
Nasca *et al.* [65]	1	1.0	1.0	0.8		1*	0.7	0.6	0.6	1.1
Tzonou *et al.* [66]		1*		0.7						
Lesher *et al.* [67]										
—unadjusted	1*	0.9	0.7		0.6	1*	0.8	1.2	1.2	
—adjusted‡	1*	0.9	0.7		0.5	1*	0.8	1.1	0.9	
Voigt *et al.* [68]										
—unadjusted	1*	0.9	0.7		0.8	1*	1.0	0.8	1.2	
—adjusted‡	1*	0.8	0.7		0.6	1*	0.9	0.6	1.0	
Mori *et al.* [70]	1*		1.1		0.4					
Kvale *et al.* [71]§										
—unadjusted	1.5	1.0	0.9	0.8	0.6†	0.7	0.9	0.9	1.4	1.0
—adjusted‡	1.4	1.0	0.9	0.9	0.7†	0.8	1.0	0.9	1.3	0.8
Wu *et al.* [72]	1*	0.9		0.9		1*	1.3	1.0	1.3	

*Reference category.
†$P < 0.05$
‡Adjusted for parity or age at first birth, as appropriate.
§Cohort study.

Table 5. Endometrial cancer and ages at first and last birth in Norway [33]

		Model 1*	Model 2*
Age at first birth (≥35 vs. <20 years)	Relative odds estimate	0.48	0.66
	P values for linear trend	<0.01	NS
Age at last birth (≥40 vs. <25 years)	Relative odds estimate	0.45	0.56
	P values for linear trend	<0.01	NS

*Estimate from multiple logistic regression, allowance was made for:
Model 1: age at first or last birth, age, urban–rural place of residence and parity;
Model 2: age at first and last birth, age, urban–rural place of residence and parity excluding women with <2 full-term deliveries.

four case-control studies [55, 58, 59, 64]. Since multiply pregnant women usually start reproduction early in their life, independent effects of age at first pregnancy and number of pregnancies are difficult to establish. La Vecchia *et al.* [64] found a significant excess risk associated with late age at first birth after adjustment for parity. Conversely, low parity was not significantly associated with ovarian cancer risk after adjustment for age at first birth [64]. In three case-control studies [62, 67, 68] and one prospective investigation [71] no relationship with age at first birth remained after adjustment for parity. Several other investigations did not find a consistent increase in risk of ovarian cancer with increasing age at first pregnancy [62, 65]. The possibility of such an association is further weakened by the aforementioned correlational study [53] where no association with age at first birth or average age at childbirth could be seen.

In conclusion, the effect of age at first pregnancy on ovarian cancer risk must be weak, if any. However, it is worth remembering also that the relative risk estimates for increasing number of children, after exclusion of nulliparous women, tend to be very close to unity (see also, for a review, Greene *et al.* [73]), in most instances not significantly below it (Table 3). This issue, therefore, in addition to that concerning the separate effect parity and fertility, deserves larger and better designed studies, particularly for its potential in elucidating the mechanisms of ovarian carcinogenesis.

Incessant ovulation and gonadotrophins

Most factors which seem to lower ovarian cancer risk suppress ovulation. Indeed, ovulation exposes the ovarian epithelium to recurrent minor trauma and contact with follicular fluid. The 'incessant

ovulation' theory, first described by Fathalla [74], has undoubtedly the merits of attracting attention to one of the most striking recent changes in present day women's reproductive experience. The subsequent model based on 'ovulatory age' (i.e. period from starting to cessation of menses minus 'protected time' constituted by pregnancies and OC use) is not, however, at least at its present state [1], satisfactory, perhaps on account of different proportions of ovulatory years at different ages.

Others [62] have suggested that pregnancy, as well as OC use, may protect against ovarian cancer by reducing total exposure to pituitary gonadotrophins. The lack of protection from use of estrogen therapy [63] provides, however, evidence against the importance of gonadotrophin stimulation. The two best recognized risk factors for ovarian cancer (i.e. nulliparity and lack of oral contraceptive (OC) use [75]) certainly remain open to different interpretations, as shown by their importance in the etiology of other hormone-dependent tumors [75].

ENDOMETRIAL CANCER

The hypothesis that the continuous influence of estrogenic substances not alternated by progesterone is causally related to endometrial cancer had already been clearly formulated in the 1950s [76]. At the moment, the understanding of the basic hormonal biology of endometrial cancer is far more advanced than that of any other gynecological malignancy. Anything that increases exposure of endometrium to unopposed estrogen increases the risk of the disease for the rest of a woman's life by increasing the frequency of mitosis and subsequent copying errors in the endometrium [77]. Conversely, anything that decreases exposure decreases the risk [77]. Reproductive factors must be considered in this framework although it must be stressed that their role in relation to endometrial cancer has received far less attention than the influence of exogenous estrogens and obesity.

Pregnancy and fertility

Before the menopause, the normal levels of estradiol are so high that endometrial activity is stimulated to the maximum and small increases have no effect on the risk of endometrial cancer [77]. What does affect the risk is change in the duration of unopposed estrogen exposure. The endometrium of a women with 'normal' ovulatory cycles proliferates for 14 days in the cycle, i.e. for some 50% of the time. During pregnancy, as well as during OC use, the time of exposure to unopposed estrogen is reduced and this may explain the protection observed in multiparous women [77].

Nulliparous women seem to be at increased risk of endometrial cancer in most epidemiological investigations [33, 78–96]. A decrease in risk with an increasing number of childbirths after the first has also been reported, but less consistently [33, 79, 80, 83, 86, 87, 90–94]. In some studies, however, the protective effect of parity seemed to be largely restricted to the first full-term pregnancy, risk estimates not being substantially lower with increasing numbers of births [89, 95, 96]. In a case-control investigation conducted in the Northern part of Italy, the point estimate for nulliparity increased appreciably when allowance was made for marital status [89], thus suggesting that infertility and not nulliparity *per se* could be related to the risk of endometrial cancer. Other studies [33], however, have shown no difference or only moderately increased risk among ever married nulliparous women.

In young women, a strong direct association between endometrial cancer and the Stein Leventhal syndrome as well as other conditions involving infertility has been shown several times [76, 94]. The endometrium of a woman with progesterone deficiency proliferates for considerably more than 50% of the time [77]. Such a condition is very frequent in premenopausal obese women and manifests itself with amenorrhea and irregular menstrual cycles [76].

Age at pregnancy

So far, little attention has been paid to the role of age at first and subsequent pregnancies on risk of endometrial cancer. Most epidemiological studies have shown no relation either with age at first [79, 83, 86, 87, 89, 94, 96] or last birth [94, 96].

Recently, however, a significant inverse association with age at first and last birth emerged from a prospective investigation [33]. Since, as expected, parity exerted a negative confounding effect in the relationship with age at first birth, the inverse association reached statistical significance only after adjustment for parity. This was supposed to be the reason of the discrepancy with previous studies, most of which did not present results adjusted for parity [33]. Kvale *et al.* [33] admitted the difficulty of separating completely the effects of age at first and last births, but concluded, in analogy with what had been found for breast cancer [28], that age at every pregnancy may have an independent effect also on endometrial cancer and that low risk may particularly derive from late births.

Incomplete pregnancies showed in this prospective study [33], as well as in most previous epidemiological work, no notable association with risk of endometrial cancer.

CONCLUSIONS

When assessing the large number of studies on reproductive factors and breast cancer it becomes clear that the effect of parity is not simple and seems to depend strongly on how many births take place

and at what age. Despite the many thousands of subjects involved, the question of which is the strongest pregnancy-related risk factor for breast cancer still has no answer. In addition, reproductive factors are frequently related to different indicators of socio-economic status, which may be associated with other, possibly stronger, determinants of breast cancer risk.

Progress in the understanding of the etiology of breast cancer thus requires new well-designed, large, population-based epidemiological investigations, able to obtain with greater precision not only information on reproductive history, but also potential confounding factors (e.g. socio-economic status, dietary habits, etc.). Improvements in the definition of biologically homogeneous groups of breast cancer cases, on the basis of the hormone dependence and the cell-type of origin of the tumor, or age at cancer diagnosis may also be of great importance.

The studies of the association between reproductive factors and cancers of the ovary and endometrium not only present the foregoing theoretical problems, but also suffer from a substantial lack of power, on account of the relatively small numbers of subjects involved and the absence of comprehensive meta-analyses. Paradoxically, the lesson from the investigations on pregnancy-related events and breast cancer risk is that initially a decrease of old certainties must be expected to derive from the accumulation of new, better epidemiological data.

Acknowledgements—I am grateful to Prof. Carlo La Vecchia and Dr. Peter Boyle for their advice and Mrs Anna Redivo and Ilaria Calderan for preparing the manuscript. This investigation was supported by the European Organization for Cooperation in Cancer Prevention Studies (ECP) and the Italian Association for Cancer Research (AIRC), Milan.

REFERENCES

1. Pike MC. Age-related factors in cancers of the breast, ovary and endometrium. *J Chron Dis* 1987, **40**, 59S–69S.
2. Dao TL. The role of ovarian steroid hormones in mammary carcinogenesis. In: Pike MC, Siiteri PK, Welsch CW, eds. *Hormones and Breast Cancer*. Banbury Report No. 8, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1981, 281–298.
3. Welsch CW. Prolactin and growth hormone in the development, progression and growth of murine mammary tumors. In: Pike MC, Siiteri PK, Welsch CW, eds. *Hormones and Breast Cancer*. Banbury Report No. 8, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1981, 299–315.
4. Boyle P. Epidemiology of breast cancer. *Baillière's Clin Oncol* 1988, **2**, 1–57.
5. MacMahon B, Cole P, Lin TM *et al.* Age at first birth and breast cancer risk. *Bull WHO* 1970, **43**, 209–221.
6. La Vecchia C, Negri E, Boyle P. Reproductive factors and breast cancer: an overview. *Soc Prevent Med* 1989, **34**, 101–107.
7. Choi NW, Howe GR, Miller AB *et al.* An epidemiologic study of breast cancer. *Am J Epidemiol* 1978, **107**, 510–521.
8. Herity BA, O'Halloran MJ, Bourke GJ, Wilson-Davis K. A study of breast cancer in Irish women. *Br J Prevent Soc Med* 1975, **29**, 178–181.
9. MacMahon B, Purde M, Cramer D, Hint E. Association of breast cancer risk with age at first birth and subsequent births: a study in the population of the Estonian Republic. *JNCI* 1982, **69**, 1035–1038.
10. Trapido EJ. Age at first birth, parity and breast cancer risk. *Cancer* 1983, **51**, 946–948.
11. Brinton LA, Hoover R, Fraumeni JF Jr. Reproductive factors in the aetiology of breast cancer. *Br J Cancer* 1983, **47**, 757–762.
12. Talamini R, La Vecchia C, Franceschi S *et al.* Reproductive and hormonal factors and breast cancer in a Northern Italian population. *Int J Epidemiol* 1985, **14**, 70–74.
13. Brignone G, Cusimano R, Dardanoni G *et al.* A case-control study on breast cancer risk factors in a Southern European population. *Int J Epidemiol* 1987, **16**, 356–361.
14. Adami H-O, Rimsten A, Stenkvist B, Vegelius J. Reproductive history and risk of breast cancer. *Cancer* 1978, **41**, 747–757.
15. Thein-Hlaing, Thein-Maung-Myint. Risk factors of breast cancer in Burma. *Int J Cancer* 1978, **21**, 724–730.
16. Adami H-O, Hansen J, Jung B, Rimsten AJ. Age at first birth, parity and risk of breast cancer in a Swedish population. *Br J Cancer* 1980, **42**, 651–658.
17. Paul C, Skegg DCG, Spears GFS, Kaldor JM. Oral contraceptive and breast cancer: a national study. *Br Med J* 1986, **293**, 723–731.
18. Rosero-Bixby L, Oberle MW, Lee NC. Reproductive history and breast cancer in a population of high fertility, Costa Rica, 1984–85. *Int J Cancer* 1987, **40**, 747–754.
19. Ewertz M, Duffy SW. Risk factors of breast cancer in relation to reproductive factors in Denmark. *Br J Cancer* 1988, **58**, 99–104.
20. Soini I. Risk factors of breast cancer in Finland. *Int J Epidemiol* 1977, **6**, 365–373.

21. Tulinius H, Day NE, Johannesson G, Bjarnason O, Gonzales M. Reproductive factors and risk for breast cancer in Iceland. *Int J Cancer* 1978, **21**, 724–730.
22. Paffenbarger RS, Kampert JB, Chang HG. Characteristics that predict risk of breast cancer before and after the menopause. *Am J Epidemiol* 1980, **112**, 258–268.
23. Bain C, Willett W, Rosner B, Speizer FE, Belanger C, Hennekens ChH. Early age at first birth and decreased risk of breast cancer. *Am J Epidemiol* 1981, **114**, 705–709.
24. Helmrich SP, Shapiro S, Rosenberg L *et al.* Risk factors for breast cancer. *Am J Epidemiol* 1983, **117**, 35–45.
25. Toti A, Agugiaro S, Amadori D *et al.* Breast cancer risk factors in Italian women: a multicentric case-control study. *Tumori* 1986, **72**, 241–249.
26. Pathak DR, Speizer FE, Willet WC, Rosner B, Lipnick RJ. Parity and breast cancer risk: possible effect on age at diagnosis. *Int J Cancer* 1986, **37**, 21–25.
27. Kvale G, Heuch I, Eide GE. A prospective study of reproductive factors and breast cancer. I. Parity. *Am J Epidemiol* 1987, **126**, 831–841.
28. Kvale G, Heuch I. A prospective study of reproductve factors and breast cancer. II. Age at first and last birth. *Am J Epidemiol* 1987, **126**, 842–850.
29. La Vecchia C, Decarli A, Parazzini F *et al.* General epidemiology of breast cancer in Northern Italy. *Int J Epidemiol* 1987, **16**, 347–355.
30. Schatzkin A, Palmer JR, Rosenberg L *et al.* Risk factors for breast cancer in black women. *JNCI* 1987, **78**, 213–217.
31. Yuan J-M, Yu MC, Ross RK, Gao Y-T, Henderson BE. Risk factors for breast cancer in Chinese women in Shanghai. *Cancer Res* 1988, **48**, 1949–1953.
32. Tao SC, Yu MC, Ross RK, Xiu KW. Risk factors for breast cancer in Chinese women of Beijing. *Int J Cancer* 1988, **42**, 495–498.
33. Kvale G, Heuch I, Ursin G. Reproductive factors and risk of cancer of the uterine corpus: a prospective study. *Cancer Res* 1988, **48**, 6217–6221.
34. Lilienfeld A, Coombs J, Bross IDJ. Marital and reproductive experience in a community-wide epidemiological study of breast cancer. *John Hopkins Med J* 1975, **136**, 157–162.
35. De Waard F, Trichopoulos D. A unifying concept of the aetiology of breast cancer. *Int J Cancer* 1988, **41**, 666–669.
36. Trichopoulos D, Hsieh C-C, MacMahon B *et al.* Age at any birth and breast cancer risk. *Int J Cancer* 1983, **31**, 701–704.
37. Woods KL, Smith SR, Morrison JM. Parity and breast cancer: evidence of a dual effect. *Br Med J* 1980, **281**, 419–422.
38. Byers T, Graham S, Rzepka T, Marshall J. Lactation and breast cancer. Evidence for a negative association in premenopausal women. *Am J Epidemiol* 1985, **121**, 664–674.
39. McTiernan A, Thomas DB. Evidence for a protective effect of lactation on risk of breast cancer in young women. *Am J Epidemiol* 1986, **124**, 353–358.
40. Kaplan SD, Acheson RM. A single etiologic hypothesis for breast cancer? *J Chron Dis* 1966, **19**, 1221–1230.
41. Salber EJ, Trichopoulos D, MacMahon B. Lactation and reproductive histories of breast cancer patients in Boston, 1965–66. *JNCI* 1969, **43**, 1013–1024.
42. Valaoras VG, MacMahon B, Trichopoulos D *et al.* Lactation and reproductive histories of breast cancer patients in Greater Athens. *Int J Cancer* 1969, **4**, 350–363.
43. Ravnihar B, MacMahon B, Lindtner J. Epidemiologic features of breast cancer in Slovenia, 1965–1967. *Eur J Cancer* 1971, **7**, 295–306.
44. Lin TM, Chen KP, MacMahon B. Epidemiologic characteristics of cancer of the breast in Taiwan. *Cancer* 1971, **27**, 1497–1504.
45. Yuasa S, MacMahon B. Lactation and reproductive history of breast cancer patients in Tokyo, Japan. *Bull WHO* 1970, **42**, 195–204.
46. Lowe CR, MacMahon B. Breast cancer and reproductive history of women in South Wales. *Lancet* 1970, **i**, 153–157.
47. Mirra AP, Cole P, MacMahon B. Breast cancer in an area of high parity: Sao Paulo, Brazil. *Cancer Res* 1971, **31**, 77–83.
48. Kalache A, Vessey MP, McPherson K. Lactation and breast cancer. *Br Med J* 1980, **1**, 223–224.
49. Lubin JH, Burns PE, Blot WJ *et al.* Risk factors for breast cancer in women in northern Alberta, Canada, as related to age at diagnosis. *JNCI* 1982, **68**, 211–217.
50. Anderson JD. Breast feeding and breast cancer. *S Afr Med J* 1975, **49**, 479–482.
51. Pike MC, Henderson BE, Casagrande JT, Rosario I, Gray GE. Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer* 1981, **43**, 72–79.
52. Wynder EL, Dodo H, Barber HRK. Epidemiology of cancer of the ovary. *Cancer* 1969, **23**, 352–370.
53. Beral V, Fraser P, Chilvers C. Does pregnancy protect against ovarian cancer? *Lancet* 1978, **i**, 1083–1087.
54. Weiss NS. Measuring the separate effects of low parity and its antecedents on the incidence of ovarian cancer. *Am J Epidemiol* 1988, **128**, 451–455.
55. Joly DJ, Lilienfeld AM, Diamond EL, Bross IDJ. An epidemiologic study of the relationship

of reproductive experience to cancer of the ovary. *Am J Epidemiol* 1974, **99**, 190–209.
56. Newhouse ML, Pearson RM, Fullerton JM, Boesen EA, Shannon HS. A case control study of carcinoma of the ovary. *Br J Prevent Soc Med* 1977, **31**, 148–153.
57. Casagrande JT, Louie EW, Pike MC, Roy S, Ross RK, Henderson BE. 'Incessant ovulation' and ovarian cancer. *Lancet* 1979, **ii**, 170–173.
58. McGowan L, Parent L, Lednar W, Norris HJ. The women at risk for developing ovarian cancer. *Gynecol Oncol* 1979, **7**, 325–344.
59. Hildreth NG, Kelsey J, Livolsi VA *et al.* An epidemiologic study of epithelial carcinoma of the ovary. *Am J Epidemiol* 1981, **114**, 398–405.
60. Franceschi S, La Vecchia C, Helmrich SP, Mangioni C, Tognoni G. Risk factors for epithelial ovarian cancer in Italy. *Am J Epidemiol* 1982, **115**, 714–719.
61. Rosenberg L, Shapiro S, Slone D *et al.* Epithelial ovarian cancer and combination oral contraceptives. *JAMA* 1982, **247**, 3210–3212.
62. Cramer DW, Hutchison GB, Welch WR, Scully RE, Ryan KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *JNCI* 1983, **71**, 711–716.
63. Risch HA, Weiss NS, Lyon JL, Daling JR, Liff JM. Events of reproductive life and the incidence of epithelial ovarian cancer. *Am J Epidemiol* 1983, **117**, 128–139.
64. La Vecchia C, Decarli A, Franceschi S, Regallo M, Tognoni G. Age at first birth and the risk of epithelial ovarian cancer. *JNCI* 1984, **73**, 663–666.
65. Nasca PC, Greenwald P, Chorost S, Richart R, Caputo T. An epidemiologic case-control study of ovarian cancer and reproductive factors. *Am J Epidemiol* 1984, **119**, 705–713.
66. Tzonou A, Day NE, Trichopoulos D *et al.* The epidemiology of ovarian cancer in Greece: a case-control study. *Eur J Cancer Clin Oncol* 1984, **20**, 1045–1052.
67. Lesher L, McGowan L, Hartge P, Hoover R. Letter to the Editor. Age at first birth and risk of epithelial ovarian cancer. *JNCI* 1985, **74**, 1361–1362.
68. Voigt LF, Harlow BL, Weiss NS. The influence of age at first birth and parity on ovarian cancer risk. *Am J Epidemiol* 1986, **124**, 490–491.
69. Lee NC, Wingo PA, Gwinn ML *et al.* The reduction in risk of ovarian cancer associated with oral-contraceptive use. *N Engl J Med* 1987, **316**, 650–655.
70. Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK. Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am J Epidemiol* 1988, **128**, 771–777.
71. Kvale G, Heuch I, Nilssen S, Beral V. Reproductive factors and risk of ovarian cancer: a prospective study. *Int J Cancer* 1988, **42**, 246–251.
72. Wu ML, Whittemore AS, Paffenbarger RS Jr *et al.* Personal and environmental characteristics related to epithelial ovarian cancer. I. Reproductive and menstrual events and oral contraceptive use. *Am J Epidemiol* 1988, **128**, 1216–1227.
73. Greene MH, Clark JW, Blayney DW. The epidemiology of ovarian cancer. *Semin Oncol* 1984, **11**, 209–226.
74. Fathalla MF. Factors in the causation and incidence of ovarian cancer. *Obstet Gynecol Surv* 1972, **27**, 751–768.
75. La Vecchia C, Decarli A, Fasoli M *et al.* Oral contraceptives and cancers of breast and of the female genital tract. Interim results from a case-control study. *Br J Cancer* 1986, **54**, 311–317.
76. De Waard F. On the aetiology of endometrial carcinoma. *Acta Endocrinol* 1958, **29**, 279–294.
77. Key TJA, Pike MC. The dose–effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 1988, **57**, 205–212.
78. Logan WPD. Marriage and childbearing in relation to cancer of the breast and uterus. *Lancet* 1953, **ii**, 1199–1202.
79. Stewart HL, Dunham LJ, Casper J *et al.* Epidemiology of cancers of uterine cervix and corpus, breast and ovary in Israel and New York City. *JNCI* 1966, **37**, 1–95.
80. Dunn LJ, Bradbury JT. Endocrine factors in endometrial carcinoma. *Am J Obstet Gynecol* 1967, **97**, 465–471.
81. Fox H, Sen DK. A controlled study of the constitutional stigmata of endometrial adenocarcinoma. *Br J Cancer* 1970, **24**, 30–36.
82. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med* 1975, **293**, 1167–1170.
83. Elwood JM, Cole P, Rothman KJ, Kaplan SD. Epidemiology of endometrial cancer. *JNCI* 1977, **59**, 1055–1060.
84. McDonald TW, Annegers JF, O'Fallon WM, Dockerty MB, Malkasian GD, Kurland LT. Exogenous estrogen and endometrial carcinoma: case-control and incidence study. *Am J Obstet Gynecol* 1977, **127**, 572–580.
85. Hulka BS, Grimson RC, Greenberg BC *et al.* 'Alternative' controls in a case-control study of endometrial cancer and exogenous estrogen. *Am J Epidemiol* 1980, **112**, 376–387.
86. Miller AB, Barclay THC, Choi NW *et al.* A study of cancer, parity and age at first pregnancy. *J Chron Dis* 1980, **33**, 595–605.
87. Kelsey JL, LiVolsi VA, Holford TR *et al.* A case-control study of cancer of the endometrium. *Am J Epidemiol* 1982, **116**, 333–342.

88. Beral V. Long term effects of childbearing on health. *J Epidemiol Commun Health* 1985, **39**, 343–346.
89. La Vecchia C, Franceschi S, Decarli A, Gallus G, Tognoni G. Risk factors for endometrial cancer at different ages. *JNCI* 1984, **73**, 667–671.
90. Pettersson B, Adami HO, Bergstrom R, Jahansson EDB. Menstrual span—a time-limited risk factors for endometrial carcinoma. *Acta Obstet Gynecol Scand* 1986, **65**, 247–255.
91. The Cancer Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. Combination oral contraceptive use and the risk of endometrial cancer. *JAMA* 1987, **257**, 796–800.
92. Beral V. Parity and susceptibility to cancer. In: *Ciba Foundation Symposium. Fetal Antigens and Cancer*. London, Pitman 1983, **96**, 182–203.
93. Plesko I, Preston-Martin S, Day NE, Tzonou A, Dimitrova E, Somogy J. Parity and cancer risk in Slovakia. *Int J Cancer* 1985, **36**, 529–533.
94. Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in young women. *Br J Cancer* 1983, **47**, 749–756.
95. Salmi T. Risk factors in endometrial carcinoma with special reference to the use of estrogens. *Acta Obstet Gynecol Scand* 1979, Suppl, 1–119.
96. Wynder EL, Escher GC, Mantel N. An epidemiological investigation of cancer of the endometrium. *Cancer* 1966, **19**, 489–520.
97. Boyle P, Leake R. Progress in understanding breast cancer: epidemiological and biological interactions. *Breast Cancer Res Treat* 1988, **11**, 91–112.